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Platelet-rich fibrin and its use in dentistry

Trombositten zengin fibrin ve diş hekimliğinde kullanımı

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ABSTRACT

PRF is often defined as an autogenous fibrin biomaterial rich in leukocytes and platelets and is clinically easy to obtain and use. Various methods are available to prepare platelet concentrates, albeit the contents of platelet concentrates obtained by different methods also vary. Accordingly, they are divided into P-PRF, L-PRF, i-PRF, A-PRF, and A-PRF+, considering the thrombocyte leukocyte concentrates and fibrin contents. PRF is widely adopted in dentistry as promoting angiogenesis, immunity, and epithelial proliferation.

Keywords: PRF, P-PRF, L-PRF, i-PRF, A-PRF, A-PRF+

ÖZ

TZF, lökositten ve trombositten zengin otojen bir fibrin biyomateryali olarak tanımlanmıştır . TZF'nin elde eldilmesi ve klinik kullanımı kolaydır. Trombosit konsantrelerinin hazırlanmasında değişik yöntemler mevcuttur. Farklı yöntemlerle elde edilen trombosit konsantrelerinin içeriği de farklıdır. Buna göre trombosit lökosit konsantrelerinin ve fibrin içerikleri göz önünde bulundurularak S-TZF, L-TZF, E-TZF, G-TZF ve G-TZF+ olarak gruplara ayrılmaktadır. TZF, anjiojenez, bağışıklık ve epitel proliferasyonu desteklediği için diş hekimliğinde yaygın bir şekilde kullanılmaktadır.

Anahtar Kelimeler: TZF, S-TZF, L-TZF, E-TZF, G-TZF, G-TZF+

INTRODUCTION

The use of platelet concentrations in medicine was initiated in the 1990s and has expanded until today. Platelets are cells that initiate and promote wound healing by releasing various growth factors. Such growth factors create signals stimulating cell proliferation and affect connective tissue healing, bone regeneration and repair, increase in mitogenesis of fibroblasts and angiogenesis of the wound site, and macrophage activation (29). The use of growth factors to contribute to wound healing has been found to be rather interesting, and thus, many platelet-derived blood products have been developed using different techniques. Yet, the literature has conceptual confusion since different platelet-derived blood products, in other words, platelet-derived blood concentrations, are called by similar names. All available platelet-rich plasma (PRP) methods bear some common aspects. Blood is drawn with anticoagulant just before surgery and immediately centrifuged. Platelet concentration preparation time is variable but is always accomplished within an hour. The first centrifugation step separates the blood into three layers: while red blood cells are at the very bottom layer, acellular plasma (platelet-poor plasma) occupies the top layer. The thrombocyte-rich buffy coat is found between these two layers. Finally, the platelet concentrate is administered to the surgical site through an injector with thrombin and/or calcium chloride (or similar factors) to trigger platelet activation and fibrin polymerization (13).

PRF, on the other hand, is the latest developed of these protocols. In this protocol, blood is drawn without any anticoagulant and immediately centrifuged. A natural coagulation process is allowed, and L-PRF is easily collected without the intervention of any biochemical agent in the blood (i.e., without the need for anticoagulants, thrombin, or calcium chloride) (12). This open-intervention method is considered the simplest and lowest-cost one ever developed (15).

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Choukroun's Platelet-rich Fibrin

The PRF protocol was first described by Choukroun in France in 2001 and introduced in the review series published by Dohan et al. (7) in 2006. PRF is a second-generation platelet concentrate that allows for obtaining a membrane rich in platelets and growth factors. The protocol is not dependent on a medical device or specialized machine and can be easily adopted. Unlike fibrin glue or PRP, it is not a blood-derived product. Venous blood is collected into dry glass tubes and centrifuged at a low speed [about 400g: 3000 rpm-10 min. or 2700 rpm-12 min.]. Since no anticoagulant is given to the blood in PRF, clotting begins as soon as the blood contacts the tube (10). Platelet activation and fibrin polymerization are promptly triggered in the absence of anticoagulants. Fibrinogen is initially formed at the neck of the tube before circulating thrombin converts it to fibrin and then gathers in the middle. Platelets are theoretically trapped in the fibrin mesh; therefore, three layers are formed after centrifugation: red blood cells at the bottom, acellular plasma at the top, and PRF clot in the middle. PRF clot generates a strong fibrin matrix with a complex three-dimensional structure in which most of the clot, leukocytes, and platelets are concentrated (11).

The success of the method relies entirely on the rate of collection and centrifugation of blood since the only way to achieve a clinically usable PRF is to act quickly. If not treated quickly enough, the fibrin will likely polymerize, and the resulting product will contain negligible fibrin mesh. A clinically usable PRF has serum and platelets trapped in the fibrin mesh. When serum from the fibrin clot is removed, a highly resistant autologous fibrin membrane will remain between two sponges. The previous research reported the use of this autologous biomaterial in maxillofacial and plastic surgery and implant surgery (31).

In this method, the fibrin mesh obtained by slow centrifugation of blood is ensured to be three-dimensional and flexible, allowing cytokine and cell migration (12).

Unlike PRP, PRF does not dissolve immediately after administration and forms slowly, similar to a natural blood clot. This method allows for the collection of platelets and leukocytes with high efficiency and preservation of leukocytes. In addition, platelets are activated during the process, which helps platelet and leukocyte growth factors to be absorbed into the fibrin matrix (12). This method ensures obtaining high volumes of PRF for more extensive operations using an eight-tube centrifuge or any modified laboratory centrifuge. The method is also low-cost and convenient; therefore, it becomes advantageous for widespread use in daily practice (15).

PRF Content

PRF obtained by centrifugation of blood taken with a standard 10 ml syringe contains all the components found in 10 ml blood:

- Platelets
- Platelet growth factors
- Leukocytes
- Cytokines
- Fibrin
- Circulating stem cells.

Platelets are discoidal and anucleated cells with a lifespan of 8-10 days, and their cytoplasm has granules to be released into the environment when activated. β-granules contain specific (such as β-thrombomodulin) and non-specific (fibronectin, thrombospondin, fibrinogen, other coagulation factors, growth factors, fibrinolysis inhibitors, and immunoglobulins) products. They need to be activated to initiate and support hemostasis in the wound area. As a result of their degranulation, they also provide the release of cytokines and growth factors that initiate the first phase of wound healing within the fibrin matrix. Following centrifugation, platelets are only found in the region of the PRF clot. The previous research demonstrated that platelets are particularly dense at the junction of the PRF and the red clot where the red blood cells are concentrated. The absence of anticoagulants in the blood during PRF formation allows for intense platelet activation in the glass tube, resulting in the release of platelet cytokines and growth factors. These cytokines are then trapped in the flexible fibrin mesh emerging due to slow polymerization. Glycosaminoglycans (heparin, hyaluronic acid) are also embedded in the PRF matrix; they are histologically bound to the fibrillar structure of fibrin. The binding power of glycosaminoglycans to small circulating peptides is relatively strong, and their capacity to support cell migration and healing is pretty high (12). Choukroun, a developer of PRF, further modified it to an advanced form (A-PRF), which is expected to contain a relatively greater number of white blood cells (WBC). Because of low-speed centrifugation, this fibrin clot is softer than that of the original PRF. On the other hand, concentrated growth factors (CGF), another modified form of PRF, are prepared by repeatedly switching the centrifugation speed and are characterized as a relatively stiffer fibrin clot. Therefore, it has been anticipated that the difference in mechanical characteristics may produce a difference in the growth factor content (40).

PLATELET GROWTH FACTORS

Transforming Growth Factor - β1 (TGF-β1)

TGF-β is a very large superfamily with more than 30 members, and its most produced isoform is TGF-β1.

TGF-β1 is produced not only from the α granules of platelets but also in intercellular communication. Its effects vary by the amount applied, matrix circumference, and cell type. For example, it can easily inhibit the proliferation of osteoblasts as well as boosts them. It is considered the most potent fibrosis agent among all cytokines (5). It contributes to collagen-1 production in osteoblasts and fibroblasts (fibrosis) and is considered an inflammatory regulator thanks to its capacity to induce fibrous healing.

Platelet-derived Growth Factor (PDGF)

PDGFs are highly needed for the migration, proliferation, and survival of mesenchymal cells. Depending on the distribution of their specific receptors, they can either stimulate or inhibit the growth of these cells. They play a role in embryonic development and regeneration mechanisms in all tissues; therefore, they assume a key role in physiological recovery and pathogenesis of atherosclerosis and many other fibroproliferative diseases (e.g., neoplasms, pulmonary and renal fibrosis) (35).

Insulin-like Growth Factor (IGF)

It is knowns as a cell protective agent. IGFs are positive regulatory agents for the differentiation and proliferation of many cells, including tumor cells. Despite being proliferation mediators for cells, they are the most important cytokines regulating apoptosis by generating signals that protect cells from many apoptotic stimuli in the matrix. IGFs are found in high levels in the circulating blood, although they are secreted by platelets. A previous study revealed that IGF in PRF is not caused by platelet activation and that the highest concentration of IGF is found in plasma. In an in vitro study, TGF-β1, PDGF-BB, and IGF-1 concentrations in PRF were found to be 6.634 ng/ml, 1.419 ng/ml, and 209.68 ng/ml, respectively (13).

LEUKOCYTES

The literature on platelets often overlooks the influence of fibrin and leukocytes, two key parameters in classification. Some scholars recommend the removal of leukocytes despite the lack of scientific evidence (1). Some others, on the other hand, emphasize leukocytes in platelet concentrations because of their essential role as anti-infectious agents and in immune regulation (19).

CYTOKINES

Inflammatory Cytokines

The number of cytokines involved in inflammation is quite large. The most prominent of these are known to be IL-1β, IL-6, and TNF-α. IL-1β has a vital role in the control of inflammation. T-Helper provides lymphocyte stimulation. It also prevents the bone formation and increases its destruction together with TNF-α. TNF-α increases inflammatory cell phagocytosis and cytotoxicity capacity and the synthesis of IL-1 and IL-6. IL-6 is a differentiation factor for B lymphocytes and an activator for T lymphocytes and stimulates the release of antibodies (10).

Wound-healing Cytokines

Healing can be regarded from two aspects:

- Neutralization of the inflammatory signaling pathway by inhibiting its amplifications, an IL-4 function.
- Regulating and enhancing the development of initial healing structures (e.g., vasculature), a VEGF function.

The primary task of IL-4 is to support healing in inflammation. It increases collagen synthesis from fibroblasts and prevents the stimulation of MMP-1 and MMP-3 by IL-1β. It also inhibits all inflammatory signaling pathways mediated by IL-1β (23). Besides, VEGF is known to be the most potent and common vascular growth trigger. The endothelium holds a key role in cell behavior (e.g., proliferation, migration, specialization, and cell survival); even its presence is sufficient to initiate angiogenesis (22).

Like platelets, these cytokines are trapped in the fibrin mesh and released slowly during polymerization. These slow-release cytokines may suggest that PRF may be a key point in immune regulation. The cytokines in PRF also can control their own amount. A previous study investigated the amounts of IL-1β, IL-4, IL-6, TNF-α, and VEGF in the same amount of serum, PRF, and platelet-poor plasma (Dohan et al., 2006). The findings revealed that all parameters except VEGF were found in the highest amount in PRF, which refers to that slow blood activation in PRF leads to leukocyte degranulation. The increase in the number of immune cytokines indicates the defense capacity of PRF (12).

FIBRIN

Substances in PRF promote the three phenomena of soft tissue healing and maturation: angiogenesis, immunity, and epithelial closure. Angiogenesis is indeed the formation of new blood vessels in the wound. Fibrin is a natural guide for angiogenesis, and the fibrin matrix was previously shown to direct angiogenesis (10). The angiogenesis feature of the fibrin matrix can be explained by the three-dimensional structure of the fibrin gel and the activities of the cytokines trapped in the mesh. In addition, fibrin gel hosts basic fibroblast growth factor (b-FGF), VEGF, angiopoietin, and PDGF, the primary soluble factors of angiogenesis. Some studies previously documented that b-FGF and PDGF have a high affinity for fibrin (20). The binding of fibrin to some growth

factors may explain the effect of angiogenesis. An essential phase of angiogenesis is the production of αvβ3 integrin from endothelial cells. This molecule enables endothelial cells to bind to fibrin, fibronectin, and vitronectin. Fibrin increases the expression of this molecule (20).

The fibrin matrix covers the wound area by affecting epithelial cells and fibroblasts. At the wound margins, epithelial cells lose their basal and apical load and enlarge in the basal and apical direction, covering the wound. Cell migration is regulated by fibrinogen, fibronectin, tenascin, and vitronectin. The presence of fibrin, fibronectin, PDGF, and TGF-β is required to regulate integrin expression and fibroblast proliferation and migration to the wound area. Thus, PRF can be considered a fibrin-based natural biomaterial that promotes micro vascularization development and directs epithelial cell migration. It is evident that such a membrane is important to protect open wounds and accelerate healing. It also contains leukocytes, which encourage the migration of these substances. The density and content of the fibrin matrix are important parameters for any platelet concentration. A plethora of studies addressing the biological impact of platelet concentrations focus on platelet growth factors and ignore the influence of the fibrin matrix or cytokines in their environment affecting their release (11).

CIRCULATING STEM CELLS

Mesenchymal cells originating from the bone marrow participate in the regeneration of many tissues. These undifferentiated cells gather at the wound site and differentiate into different cell types. This initial differentiation occurs in the temporary wound matrix by fibrin and fibronectin; therefore, fibrin is used as a supporting matrix in the transplantation of these cells (4).

Various methods are available for preparing platelet concentrates; thus, the contents of platelet concentrates obtained by different methods are also different. Accordingly, considering the leukocyte and fibrin contents of platelet concentrates, the current classification is as follows (34):

1. Platelet-Rich Plasma (PRP)
   a. Pure Platelet-Rich Plasma (P-PRP)
   b. Leukocytes and Platelet-Rich Plasma (L-PRP)
2. Platelet-Rich Fibrin (PRF)
   a. Pure Platelet-Rich Fibrin (P-PRF)
   b. Leukocyte and Platelet-Rich Fibrin (L-PRF)
   c. Injectable PRF (i-PRF)

Pure Platelet-rich Plasma (P-PRP)

It was first developed by Anitua in 1999 (2). To obtain P-PRP, the entire cell-poor plasma layer at the top of the tube and the part of the yellowish layer in the middle section facing the cell-poor plasma are extracted through a pipette and transferred to a different tube following the very first centrifugation of the blood containing the anticoagulant agent. After the second centrifugation at a higher speed compared to the first, the cell-poor plasma layer is removed by pipetting. Then, calcium chloride is added to the remaining material in the tube to coagulate. Using only the upper part of the yellowish layer to prevent leukocytes in the product to be obtained may cause the platelet content of the material to be low. This technique of getting P-PRP is a cost-effective application to be adopted in the clinic; however, its handicap is that it is a bit challenging to prepare (15).

Leukocytes and Platelet-rich Plasma (L-PRP)

To be able to obtain L-PRP, the entire cell-poor plasma and yellowish layer and a part of the layer containing red blood cells are transferred to a new tube after the first centrifugation of the blood without the anticoagulant agent. After the second centrifugation at a higher speed compared to the first, the cell-poor plasma layer is removed by pipetting. Coagulation is ensured by adding bovine thrombin or calcium chloride to the product obtained. The amount of L-PRP obtained following these manual and time-consuming procedures is often low and quickly disappears in the tissue during healing since containing a low-density fibrin matrix. The reproducibility of the results is not reliable because the success of the technique highly relies on the person performing it (13). L-PRP was obtained differently by changing the centrifuge time and speed in the basic protocol in many studies, most of which could not introduce an explicit content of L-PRP. For example, not taking the entire yellowish layer into the second tube following the first centrifugation definitely affects the cell content and may cause P-PRP to be obtained instead of L-PRP (10).

Pure Platelet-rich Fibrin (P-PRF)

Although obtaining P-PRF is similar to getting L-PRP, the only difference is that the coagulant is added to the tube before the second centrifugation during P-PRF preparation. In this way, a denser product is obtained compared to L-PRP. Nevertheless, it is costly to obtain a sufficient amount of P-PRF to be used in the clinic with this technique, and its clinical efficacy has not yet been proven (15).

Leukocyte and Platelet-rich Fibrin (Choukroun's PRF) (L-PRF)

L-PRF is a platelet concentration involved in wound healing and immunity and includes all components of the blood (11). For the first time, it was developed

by Choukroun et al. (6) in France in 2001. Since no anticoagulant agent is needed while preparing L-PRF, it can also be considered a second-generation platelet concentrate (12). To obtain L-PRF, the blood is collected in 10 ml tubes without anticoagulant and immediately centrifuged for 10-12 minutes at about 400 g. Following centrifugation, the fibrin clot is formed in the middle of the tube. While cell-free plasma emerges at the top of the tube, red blood cells occupy the bottom. The success of the technique depends on the time spanning between collecting the blood sample and placing it in the centrifuge. Since no anticoagulant is involved when the platelets in the blood come into contact with the tube wall, platelet activation and fibrin polymerization are rapidly initiated. If the time taken for blood collection and transfer to the centrifuge is prolonged, the fibrin polymerizes dispersedly, and a small amount of non-consistent blood clot is observed (11).

L-PRF becomes a strong membrane when crushed between two hard floors, and this blood-derived biomaterial is often utilized used in oral (11), maxillofacial, otolaryngology, and plastic surgery (8) . L-PRF has the property of polymerizing naturally and slowly during centrifugation. In this technique, platelets and leukocytes are obtained in high yield, and leucocytes are preserved at every stage. Activation of platelets during the production of L-PRF ensures that platelet and leukocyte growth factors are embedded in the fibrin matrix (12). In a study, it was discovered that L-PRF contains almost all of the platelet count in the blood, the platelets are not homogeneously distributed in L-PRF, and these cells are concentrated on the fibrin side adjacent to the substrate where red blood cells accumulate in the tube (14). Dohan et al. (14) reported that growth factors (e.g., TGF-β, VEGF, and PDGF-AB) were slowly released from L-PRF for seven days. The presence of growth factors in high concentrations in the medium, therefore, allows L-PRF to stimulate the environment of wound healing. The products in this natural fibrin material bear a high potential for effect during wound healing. The key role of leukocytes in platelet concentrations was previously reported to be associated with anti-infective activity and immunomodulatory properties (17). Dohan et al. (13) investigated the amounts of IL-1b, IL-4, IL-6, TNF-α, and VEGF in platelet-poor plasma and serum with L-PRF. Accordingly, they reported that all parameters except VEGF were at the highest level in L-PRF, provided by leukocyte degranulation in L-PRF. Such an increase in cytokine levels was suggested to indicate the defense capacity of L-PRF.

L-PRF is a fibrin-based natural biomaterial that promotes micro vascularization development and directs epithelial cell migration. The relevant literature demonstrated that the fibrin matrix leads to angiogenesis (10). This feature of the fibrin matrix is explained by the three-dimensional structure of fibrin and the activities of cytokines trapped in the matrix. It was stated that b-FGF, VEGF, and PDGF show a high affinity for fibrin. On the other hand, it was suggested that fibrin acts as a supporting matrix for mesenchymal stem cells (3).

Advanced Platelets-rich Fibrin (A-PRF)

Recent years have witnessed a new protocol for PRF to further improve tissue regeneration thanks to the modification of centrifugation procedures. While standard PRF is centrifuged at 2700 rpm for 12 min., A-PRF is centrifuged at a lower rate (1500 rpm, 14 min.). This change in the centrifugation protocol was shown to increase platelet cell count and monocyte/macrophage behavior (21).

Advanced Platelet-rich Fibrin Plus (A-PRF+)

The initial procedure for PRF preparation, including a centrifugation step at 708 g relative centrifugal force-max ×12 min., is called L-PRF (11). This protocol was actually developed to activate the ex vivo coagulation process. Then, the produced fibrin matrix has a solid consistency and a dense structure with minimal space between fibrin fibers (11). There are few inflammatory cells in the matrix, but histologically they are located in the distal part of the clot. Recently, protocols for the preparation of platelet fibrin concentrates have been modified according to the "Low-speed centrifugation concept." The newest of these protocols is the A-PRF+ method (RCF-max: 208 g × 8 min.). The previous research showed that the A-PRF+ preparation gives better results; it was discovered that the number of platelets and leukocytes in the fibrin mesh is higher. Moreover, compared to L-PRF, the produced A-PRF+ fibrin matrix is more porous, providing more space for trapped platelets and immune cells and greater release of growth factors (16).

Titanium-prepared Platelet-rich Fibrin (T-PRF)

T-PRF is a novel platelet concentrate developed by Tunalı et al. (32) and utilizes titanium tubes to prevent adverse effects by the glass or glass-coated plastic tubes used in the Choukroun method to activate the platelets more. Activation of platelets with titanium compared to activation with silica particles brings many distinguishing features to T-PRF, including increased biocompatibility. Compared to the fibrin mesh in T-PRF, it was previously observed that PRF has a more robust mesh structure and longer in vivo solubility time. Thicker and tighter T-PRF is thought to cause a more polymerized fibrin formation; thus, it can stay in the tissue for a longer time (32). The T-PRF collection protocol is as follows: a blood sample is collected in 10 ml titanium tubes without anticoagulant and immediately centrifuged at 2800 rpm for 12 min.

The absence of anticoagulant leads most of the platelets to be activated within a few minutes after contact with the wall of the titanium tube, thus initiating the coagulation phase. Before circulating thrombin converts fibrinogen to fibrin, fibrinogen is accumulated at the top of the tube, and a fibrin clot forms in the middle (10). Unfortunately, the literature offers a limited number of studies on T-PRF.

Injectable PRF (i-PRF)

The way of utilizing i-PRF is often similar to PRF, but i-PRF is an injectable type. It can be used alone or in combination with other biomaterials (26), and no additives are required to produce i-PRF. It forms a small clot thanks to the presence of fibrin (26) and releases dynamic gel-containing cells and additional growth factors. i-PRF is also believed to contain stem and endothelial cells.

Areas of Use of Platelet-Rich Fibrin in Dentistry

Recent years have enjoyed increased reconstructive jaw bone surgeries thanks to the development of dental implant applications. PRF often provides convenience to the dentist and patient in pre-implant protection of extraction sockets, sinus operations, and horizontal and vertical bone augmentation applications (25). When placed in the socket following a tooth extraction, PRF accelerates healing with increased circulation and epithelialization and relatively prevents complications (e.g., alveolitis, pain, and inflammation). PRF may be advantagıus in extraction sockets as a filling material, in infected areas for new capillary vascularization and tissue reconstruction, or in systemic conditions delaying wound healing (e.g., diabetes, the use of immunosuppressants). PRF also facilitates coagulation and wound closure among patients using anticoagulants (9). Following cyst enucleation, healing is accelerated thanks to the growth factors it contains; a healing process of 6-12 months due to a blood clot is reduced to as little as two months. Together with graft materials, PRF can be used to reconstruct bone defects. In a study on rabbit parietal bone, the researchers applied no material to the defect in the control group but silk fibroin and PRF together in the experimental group. The findings revealed significantly more total new bone in the experimental group at the end of 12 weeks (27). In a study with sinus augmentation, freeze-dried bone allograft was used alone or in combination with T-PRF (29). In the group augmented with bone graft only, implants were placed at eight months, but at four months in the group with T-PRF supplement. Histomorphometric analyses revealed that the new bone formation was the same in both groups and that T-PRF could accelerate the formation of new bone. It was stated that the rich leukocytes and growth hormones in T-PRF may increase angiogenesis and contribute to the revascularization of the graft. In the same study, it was shown that the sinus membrane perforation could be permanently closed with T-PRF. Accordingly, it was proposed that the autogenous and strong fibrin matrix structure of PRF minimizes the risk of infection in perforations during healing thanks to its rich immunological structure (7). In another study, Tunalı et al. (18) documented clinical and radiographic improvement as a result of the 3-month follow-up of the autogenous bone graft and PRF applied to a tooth with an endo-perio lesion. It has been stated that the recovery is accelerated by the growth factors secreted by the platelets isolated from the blood. T-PRF was utilized as a carrier with antibiotics (e.g., high-capacity doxycycline), showing higher absorption capacity with 7-day stable activity and unique long-acting local antibacterial effect compared to collagen. Therefore, it can be confirmed that T-PRF/Doxy is a promising therapeutic agent in the treatment of periodontitis and peri-implantitis. Besides, recent research demonstrated that i-PRF has a positive and curative effect on erosive lichen planus (30). In another study, Johns et al. (36) documented that pulp revascularization shows disinfection with photodynamic therapy combined with platelet-rich fibrin leads to satisfactory root development in necrotic immature teeth. In another systematic review suggested that PRF can improve alveolar cleft reconstruction and orthodontic tooth movement (37). Pulp-capping agents such as $Ca(OH)_2$, MTA, and PRF yielded similar success rate when used in teeth with irreversible pulpitis (38). i-PRF-facilitated orthodontics is an effective and safe treatment modality to accelerate tooth movement, and this method can help shorten orthodontic treatment duration (39).

CONCLUSION

PRF demonstrated the ability to release high concentrations of various growth factors and induced high fibroblast migration. The use of PRF in dentistry is very common and successful.

ETHICAL DECLARATIONS

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REFERENCES

1. Anitua E, Sanchez M, Orive G, Andia I. The potential impact of the preparation rich in growth factors (PRGF) in different medical fields. Biomaterials 2007; 28: 4551-60.
2. Anitua E. Plasma rich in growth factors: preliminary results of use in the preparation of future sites for implants. Int J Oral Maxillofacial Implants 1999; 14: 529-35.
3. Badiavas EV, Abedi M, Butmarc J, Falanga V, Quesenberry P. Participation of bone marrow derived cells in cutaneous wound healing. J Cellular Physiology 2003; 196: 245-50.
4. Bensaıd W, Triffitt JT, Blanchat C, Oudina K, Sedel L, Petite H. A biodegradable fibrin scaffold for mesenchymal stem cell transplantation. Biomaterials 2003; 24: 2497-502.
5. Border WA, Noble NA. Transforming growth factor β in tissue fibrosis. N Engl J Med 1994; 331: 1286-92.
6. Choukroun J, Adda F, Schoeffler C, Vervelle AP. Une opportunité en paro-implantologie: le PRF. Implantodontie 2001; 42: 55-62.
7. Choukroun J, Diss A, Simonpieri A, et al. Platelet-rich fibrin (PRF): A second-generation platelet concentrate. Part IV: Clinical effects on tissue healing. Oral Surg Oral Med Oral Pathol Oral Radiol Endodontol 2006, 101: e56-60.
8. Choukroun JI, Braccini F, Diss A, Giordano G, Doglioli P, Dohan DM. Influence of platelet rich fibrin (PRF) on proliferation of human preadipocytes and tympanic keratinocytes: A new opportunity in facial lipostructure (Coleman's technique) and tympanoplasty? Revue de Laryngologie-Otologie-Rhinologie 2007; 128: 27-32.
9. Del Corso M, Toffler M, Dohan Ehrenfest DM. Use of an autologous leukocyte and platelet-rich fibrin (L-PRF) membrane in post-avulsion sites: an overview of Choukroun's PRF. J Implant Adv Clin Dent 2010; 1: 27-35.
10. Dohan DM, Choukroun J, Diss A, et al. Platelet-rich fibrin (PRF): a second-generation platelet concentrate. Part I: technological concepts and evolution. Oral Surg Oral Med Oral Pathol Oral Radiol Endodontol 2006; 101: e37-44.
11. Dohan DM, Choukroun J, Diss A, et al. Platelet-rich fibrin (PRF): A second-generation platelet concentrate. Part II: platelet-related biologic features. Oral Surg Oral Med Oral Pathol Oral Radiol Endodontol 2006; 101: e45-50.
12. Dohan DM, Choukroun J, Diss A, et al. Platelet-rich fibrin (PRF): a second-generation platelet concentrate. Part III: leucocyte activation: A new feature for platelet concentrates? Oral Surg Oral Med Oral Pathol Oral Radiol Endodontol 2006; 101: e51-5.
13. Dohan Ehrenfest DM, de Peppo GM, Doglioli P, Sammartino G. Slow release of growth factors and thrombospondin-1 in Choukroun's platelet-rich fibrin (PRF): a gold standard to achieve for all surgical platelet concentrates technologies. Growth Factors 2009; 27: 63-9.
14. Dohan Ehrenfest DM, Del Corso M, Diss A, Mouhyi J, Charrier JB. Three-dimensional architecture and cell composition of a Choukroun's platelet-rich fibrin clot and membrane. J Periodontol 2010; 81: 546-55.
15. Dohan Ehrenfest DM, Rasmusson L, Albrektsson T. Classification of platelet concentrates: from pure platelet-rich plasma (P-PRP) to leucocyte-and platelet-rich fibrin (L-PRF). Trends in Biotechnology 2009; 27: 158-67.
16. El Bagdadi K, Kubesch A, Yu X, et al. Reduction of relative centrifugal forces increases growth factor release within solid platelet-rich-fibrin (PRF)-based matrices: a proof of concept of LSCC (low speed centrifugation concept). Eur J Trauma Emerg Surg 2019; 45: 467-79.
17. El-Sharkawy H, Kantarci A, Deady J, et al. Platelet-rich plasma: growth factors and pro-and anti-inflammatory properties. J Periodontol 2007; 78: 661-9.
18. Ercan E, Suner SS, Silan C, et al. Titanium platelet–rich fibrin (T-PRF) as high-capacity doxycycline delivery system. Clin Oral Invest 2022; 26; 5429-38.
19. Everts PA, van Zundert A, Schonberger JP, Devilee RJ, Knape JT. What do we use: platelet-rich plasma or platelet-leukocyte gel? J Biomedical Materials Research Part A 2008; 85: 1135-6.
20. Feng X, Clark RA, Galanakis D, Tonnesen MG. Fibrin and collagen differentially regulate human dermal microvascular endothelial cell integrins: stabilization of αv/β3 mRNA by fibrin. J Investigative Dermatol 1999; 113: 913-9.
21. Ghanaati S, Booms P, Orlowska A, et al. Advanced platelet-rich fibrin: a new concept for cell-based tissue engineering by means of inflammatory cells. J Oral Implantology 2014; 40: 679-89.
22. Harry LE, Paleolog EM. From the cradle to the clinic: VEGF in developmental, physiological, and pathological angiogenesis. Birth Defects Research Part C: Embryo Today: Reviews 2003; 69: 363-74.
23. Hayashi Y, Kobayashi M, Kuwata H, et al. Interferon-γ and interleukin 4 inhibit interleukin 1β-induced delayed prostaglandin E2generation through suppression of cyclooxygenase-2 expression in human fibroblasts. Cytokine 2000; 12: 603-12.
24. Karde PA, Sethi KS, Mahale SA, Khedkar SU, Patil AG, Joshi CP. Comparative evaluation of platelet count and antimicrobial efficacy of injectable platelet-rich fibrin with other platelet concentrates: an in vitro study. J Indian Soc Periodontol 2017; 21: 97-101.
25. Koçyiğit İ, Tunalı M, Özdemir H, Kartal Y, Süer B. İkinci nesil trombosit konsantrasyonunun klinik uygulamalari. Cumhuriyet Dental J 2012; 15: 279-87.
26. Kour P, Pudakalkatti PS, Vas AM, Das S, Padmanabhan S. Comparative evaluation of antimicrobial efficacy of platelet-rich plasma, platelet-rich fibrin, and injectable platelet-rich fibrin on the standard strains of Porphyromonas gingivalis and Aggregatibacter actinomycetemcomitans. Contemporary Clin Dent 2017; 8: 538-44.
27. Lee EH, Kim JY, Kweon HY, et al. A combination graft of low-molecular-weight silk fibroin with Choukroun platelet-rich fibrin for rabbit calvarial defect. Oral Surg Oral Med Oral Pathol Oral Radiol Endodontol 2010; 109: e33-8.
28. Marx RE, Carlson ER, Eichstaedt RM, Schimmele SR, Strauss JE, Georgeff KR. Platelet-rich plasma: Growth factor enhancement for bone grafts Oral Surg Oral Med Oral Pathol Oral Radiol Endodontol 1998; 85: 638-46.
29. Olgun E, Ozkan SY, Atmaca HT, Yalim M, Hendek MK. Comparison of the clinical, radiographic, and histological effects of titanium-prepared platelet rich fibrin to allograft materials in sinus-lifting procedures. J Investigative Clin Dent 2018; 9: e12347.
30. Saglam E, Ozsagir ZB, Unver T, Alinca SB, Toprak A, Tunali M. Efficacy of injectable platelet-rich fibrin in the erosive oral lichen planus: A split-mouth, randomized, controlled clinical trial. J Applied Oral Sci 2021; 29: 1590-678.
31. Simonpieri A, Del Corso M, Sammartino G, Ehrenfest DM. The relevance of Choukroun's platelet-rich fibrin and metronidazole during complex maxillary rehabilitations using bone allograft. Part I: A new grafting protocol. Implant Dentistry 2009; 18: 102-11.
32. Tunalı M, Özdemir H, Küçükodacı Z, Akman S, Fıratlı E. In vivo evaluation of titanium-prepared platelet-rich fibrin (T-PRF): A new platelet concentrate. British J Oral Maxillofac Surg 2013; 51: 438-43.
33. Tunali M, Ozdemir H, Pikdoken L, Gurbuzer B, Selcuk OR. Endodontik-periodontal kombine kemik içi defektlerin tedavisinde trombositten zengin fibrin membran ile otojen kemik greftinin kombine kullanımı: olgu sunumu. Cumhuriyet Dent J 2011; 12: 43-6.

34. Varshney S, Dwivedi A, Pandey V. Antimicrobial effects of various platelet rich concentrates-vibes from in-vitro studies-a systematic review. J Oral Biol Craniofac Res 2019; 9: 299-305.
35. Yu JH, Ustach C, ChoiKim HR. Platelet-derived growth factor signaling and human cancer. BMB Reports 2003; 36: 49-59.
36. Johns, D. A, Shivashankar, V. Y, Krishnamma, S, & Johns, M.Use of photoactivated disinfection and platelet-rich fibrin in regenerative Endodontics. Journal of conservative dentistry 2014; 17: 487–90.
37. Francisco I, Fernandes MH, Vale F. Platelet-rich fibrin in bone regenerative strategies in orthodontics: a systematic review. Materials (Basel, Switzerland) 2020; 13: 1866.
38. Singh R, Singh R, Kavita K, Kommula A, Kulkarni G, Jois HS. To compare mineral trioxide aggregate, platelet-rich fibrin, and calcium hydroxide in teeth with irreversible pulpitis: a clinical study. J Pharm Bioallied Sci 2020: 436–9.
39. Erdur EA, Karakaslı K, Oncu E, Ozturk B, Hakkı S. Effect of injectable platelet-rich fibrin (i-PRF) on the rate of tooth movement. Angle Orthodont 2021; 91: 285–92.
40. Masuki, H, Okudera, T, Watanebe, T, et al. Growth factor and pro-inflammatory cytokine contents in platelet-rich plasma (PRP), plasma rich in growth factors (PRGF), advanced platelet-rich fibrin (A-PRF), and concentrated growth factors (CGF). Int J Implant Dentistry 2016, 2: 19.